

Recurrent pregnancy loss

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Recurrent pregnancy loss is a frustrating clinical dilemma for both patients and physicians because, in most cases, causes are nebulous and few treatments with proven benefit can be offered. Involved, expensive tests have frequently been proposed and their use has often filtered into clinical practice before their utility has been firmly demonstrated. Proposed causes of recurrent pregnancy loss include genetic and environmental etiologies, infectious agents, maternal congenital and acquired anatomic abnormalities, and immunologic and endocrinologic dysfunction. Appropriate management relies upon a realistic understanding of the often substantial limitations of currently available therapies.

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Introduction

Human reproduction is an inefficient process. Only approximately 20% of attempted conception cycles will result in clinical pregnancies. Furthermore, 50–75% of conceptions will result in miscarriage. Of women aspiring to conceive, 25% will suffer at least one clinically recognized early pregnancy loss during their reproductive careers. Losses comprise 15–20% of all clinically evident pregnancies, and 0.5–1% of women will meet the classical definition for recurrent pregnancy loss (RPL) by having three or more clinically recognized consecutive pregnancy losses. These women represent a proportion who simply have sporadic bad luck three times in a row, as well as women who have underlying reproductive problems predisposing to losses.

Proposed causes of recurrent pregnancy loss

After having a first miscarriage, couples inevitably ask why this happened. The most frequent known cause of sporadic spontaneous abortion (SAB) is cytogenetic abnormalities of the conceptus. Half of preimplantation embryos examined and one-third of embryos that have implanted are abnormal morphologically, which is most often the result of an underlying genetic defect.

Aside from genetic abnormalities, there are environmental causes of sporadic early pregnancy loss which could theoretically be associated with RPL if a pregnant woman was persistently exposed. Recently, chronic

exposure to video display terminals of more than 20 h each week has been proposed to be a cause of SAB. This claim has been refuted [1]. Recent studies examining the association, if any, between caffeine intake and RPL have come to opposite conclusions [2,3].

Definitive roles for cigarette smoke, alcohol, anesthetic agents, heavy metals, chloroquine, oral hypoglycemics and industrial organic solvents as contributors to pregnancy loss remain conjectural. There is some epidemiologic evidence that smoking more than 14 cigarettes/day increases the risk of aborting a euploid conceptus 1.7 times [4]. Likewise, moderate drinking during 2 days of the week may double the risk over nondrinkers of euploid abortion [5].

Genetic

Embryonic aneuploidy is the only proposed etiology of RPL for which there is general agreement. To have genetically induced RPL, couples must have abnormal genetic complements which are compatible with normal parental phenotypes and the ability to conceive, yet which persistently result in genetically abnormal conceptuses that are unable to endure. These conditions can be fulfilled when at least one member of a couple has chromosomal aberrations with either an abnormal number of chromosomes (numerical abnormalities) or rearrangements of the genetic material within the chromosomes (structural abnormalities). Moreover, to maintain normal phenotypes, these individuals must maintain complete (balanced) complements of chromosomal material,

Abbreviations

ACL—anticardiolipin; APS—antiphospholipid syndrome; APTT—activated partial thromboplastin time; DES—diethylstilbestrol; LAC—lupus anticoagulant; LPI—luteal phase inadequacy; RPL—recurrent pregnancy loss; SAB—spontaneous abortion.

or have only minimally unbalanced parental genomes. The production of unbalanced gametes during meiosis as a result of the parental structural chromosomal abnormalities yields either duplication or deficiency of chromosomal segments in the resulting conceptuses as the cause of repetitive abortions.

In a compilation of 79 cytogenetic studies of couples with two or more SABs, karyotypes from a total of 8298 women and 7834 men were reviewed [6]. At least one member of 2.9% of the couples had a detectable chromosomal abnormality, which is about five–six times the prevalence in the general population. The female partners were twice as likely to have a chromosomal abnormality than their male counterparts. Among all detectable chromosome abnormalities, 50% had balanced reciprocal translocations, 25% had Robertsonian translocations and 12% had X-chromosome mosaicism; and inversions and sporadic abnormalities made up the remainder (Fig. 1). Normally, only one in 700 phenotypically normal people will have a translocation. Data from an even larger database including 199 studies and over 29 000 persons having two or more miscarriages, found similar distributions [7]. Thus, parental chromosomal problems can predispose to RPL in three major ways, translocations, inversions and mosaicism, with translocations being the most likely.

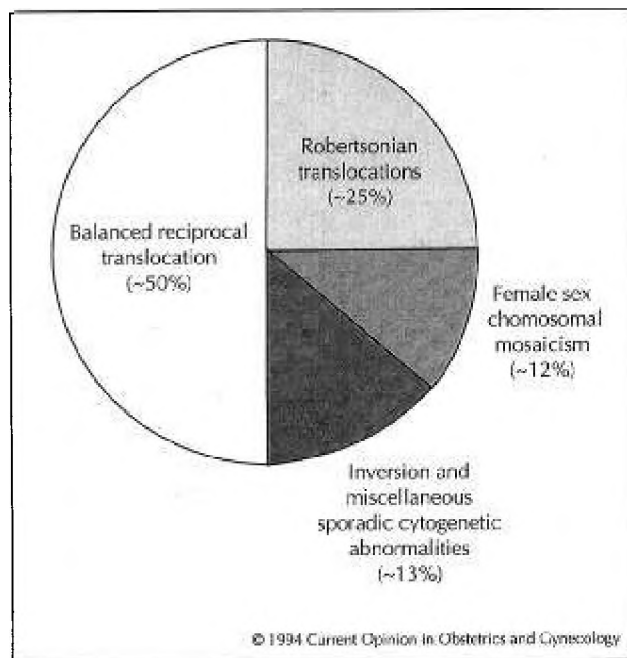


Fig. 1. Approximate proportions of karyotypic abnormalities found in individual parents when couples have two or more pregnancy losses [6].

A distinction should be made between the sporadic genetic causes of SAB and the causes of RPL attributed to parental chromosomal abnormalities. Genetic causes are easily the most common demonstrable source of sporadic abortions. About 50% of first trimester SABs

have chromosomal abnormalities. The distribution of cytogenetic abnormalities found in abortus tissue reveals that most are abnormalities of chromosome numbers (Fig. 2). Abortus specimens from RPL are expected to have a smaller proportion of chromosomal abnormalities than sporadic SABs because RPL abortuses are a select population mostly resulting from predisposing etiologies other than sporadic genetic causes. Even when abortus material from couples with RPL has karyotypic abnormalities, the abnormalities may be sporadic and do not necessarily imply an increased risk for future pregnancies. Therefore, routine cytogenetic analysis of abortus material is not currently indicated. A more fruitful approach is to evaluate parental karyotypes in couples with RPL. Unfortunately, there are no conclusive historical elements to ascertain whether a parent has a translocation or not, including having had a previous phenotypically normal child. Only karyotyping can make the diagnosis.

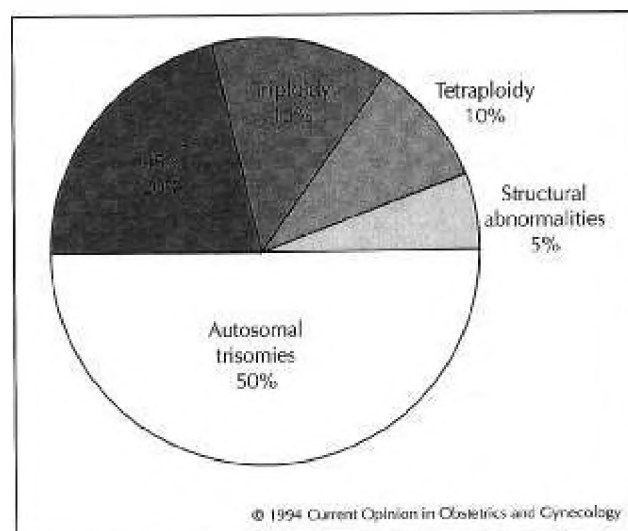


Fig. 2. Approximate distribution of cytogenetic abnormalities found in clinically recognized sporadic spontaneous abortions [8•].
* most common single chromosomal abnormality.

To date, only cytogenetic abnormalities have been detected in the search for genetic causes of RPL. Highly sensitive molecular genetic techniques now available offer the hope of uncovering subchromosomal genetic mutations as sources of RPL, as has been done in animal models. Adding support for such single gene possibilities, is a report of couples with RPL and normal karyotypes, who nonetheless have a risk higher than couples without RPL of having offspring with chromosomal abnormalities [9]. A novel example of a possible single gene defect has come to light based on case reports. Evidence shows that faulty centromere function may prematurely allow centromere division. This could be associated with chromosome instability and cell division errors as a source of RPL [10•]. Further support for the possibility of chromosome instability is provided by studies that have found methotrexate and other clasto-

gens to have increased chromosomal breakage rates in lymphocytes from couples with RPL compared with control couples [11]. Currently there are no tests for sub-chromosomal genetic mechanisms that may cause RPL.

Infectious

For an infectious agent to cause repetitive pregnancy loss, it would have to be able to exist in a chronic state. Such infections are unusual in otherwise asymptomatic women. The T strain mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*) have been proposed to cause RPL. However, mycoplasmas are highly prevalent in the cervixes of normal women, and the results of antibiotic trials have been mixed. Also, there are still no studies with culture-proven mycoplasma in abortus material.

A number of agents including viruses, bacteria, mycoplasmas, and parasites (such as toxoplasma and *Chlamydia trachomatis*) appear to be involved in sporadic losses and potentially severe pregnancy disorders, but their involvement in RPL remains unproven. Definitive roles for the utility of cervical and endometrial cultures, serological testing and alternatively, empiric antibiotic treatment for couples with RPL are lacking. These procedures should only be considered individually if there is clinical suspicion of an infectious agent precipitating recurrent losses.

Maternal anatomic abnormalities

Both congenital and acquired uterine abnormalities have been associated with RPL. Uterine anomalies have been reported to be present in up to 15% of couples with RPL. The scarcity of specific uterine abnormalities, the urgency to offer treatment when they are discovered, and the ethical problem of not offering a treatment that may have benefit, have all slowed the determination of causality of RPL. We are left with trials of therapy which are largely uncontrolled, and therefore we cannot completely assess their attributable benefit. Nevertheless, it is highly probable that incompetent cervix is a cause of RPL. By definition, an incompetent cervix does not allow a pregnancy to reach term, and this implies persistent risk with each pregnancy. Prevalence rates from <1% all the way up to 15% have been observed for couples with RPL [12]. Most studies of treatment for incompetent cervix have used women who have already experienced morbidity from an episode of cervical incompetence to serve as their own controls. This study design is vulnerable to selection bias. Nonetheless, a review of 61 such studies suggests that the chance of successful gestation in women with cervical incompetence is approximately one in four before having a cerclage procedure, and about three in four after cerclage [12]. Benefit from cerclage has not yet been confirmed in the few randomized, prospective studies conducted.

Among the numerous congenital uterine anomalies, septa have commonly been regarded as presenting the highest risk for miscarriage. However, a series of 182 women with uterine anomalies indicates that the unicornuate uterus is nearly twice as likely to be associated with SAB (approximately 50%) than septate and bicornuate uteri [13]. However, because septate uteri appear to be four or five times more common than unicornuate uteri, the septate uterus is probably the most likely Müllerian abnormality to be associated with pregnancy loss. There are few data to suggest how many SABs, if any, should be tolerated before reducing a septum. Moreover, there is still no randomized study of expectant management compared with septum reduction.

Intrauterine adhesions

It seems plausible that intrauterine adhesions can cause RPL. The degree of intrauterine adhesions required to precipitate RPL is unknown, however, so making the decision of which women with RPL to treat is subjective. No single best treatment protocol has surfaced, but March and Israel [14] observed an increased rate of pregnancy success from a baseline of 16.7% to 87.2% after hysteroscopic lysis of adhesions using microscissors followed by high-dose estrogen treatment for 2 months.

Leiomyomata uteri

As with intrauterine adhesions, a cause and effect relationship between leiomyomata and RPL is difficult to confirm. The impression that myomas may be involved in pregnancy loss again comes from nonrandomized studies which present SAB rates after myomectomy compared with the before therapy rates in select populations. Data assembled by Buttram and Reiter [15] from 1941 such women reported in seven studies show a reduction in the SAB rate from 41% to 19% following myomectomy. In practice, there are no reliable means of predicting which clinical presentations are likely to respond to myomectomy. At this time, because of serious possible morbidity, myomectomy for the indication of RPL should only be considered when all other potential etiologies have been excluded and suspicion is high that intracavitary distortion from leiomyomata are causative.

Diethylstilbestrol

Up to 1.5 million women carrying female fetuses are estimated to have taken diethylstilbestrol (DES) to battle against pregnancy loss until 1971 when the US Food and Drug Administration withdrew its approval. Investigations into the effect of DES on reproductive performance indicate an increased likelihood (up to two times) of a DES-exposed daughter to miscarry [16]. However, data are too few to implicate DES as a certain cause for RPL. Moreover, the presence of cervical abnormalities and hysterosalpingographic abnormalities attributable to

DES exposure do not predict SAB and cannot be used to dictate management [17]. Preconceptional cerclage to improve reproductive performance in DES-exposed women has not proven cost-effective. The number of DES-exposed women of reproductive age is declining and the determination of their optimal management concerning RPL will probably not be possible.

The immune factor

Because pregnancies are immunologically privileged, researchers have sought to confirm that a breach of this intricate and poorly understood phenomenon may lead to RPL. The bulk of recent research activity into the pathophysiology of RPL has focused on the immune factor. Two different categories of immune dysfunction have been scrutinized. Alloimmune refers to immunologic disparity between individuals of the same species, whereas autoimmune refers to immunologic activity against one's self.

Alloimmune

Although conceptually attractive, there are no definitive tests to prove that altered alloimmunity even exists as a cause of RPL. A popular hypothesis has been that when partners share too many human leukocyte antigens, which include the transplantation matching antigens, proper maternal recognition of their conceptus may be thwarted such that immunological protection of the fetus cannot be afforded. However, studies looking for human leukocyte antigen sharing among couples with RPL have found inconsistent associations. Furthermore, none of the alloimmune immunologic tests such as the mixed lymphocyte reaction and antileukocytotoxic antibody testing have demonstrated predictive value for pregnancy outcome in couples with RPL [18]. The tests are expensive, and presently have no practical value in the management of RPL.

Despite the lack of concrete methods to detect, predict or follow the presence of alloimmune RPL, empiric therapies have been attempted. The principal therapy for unexplained RPL, presumed to be of alloimmune origin, has been to immunize the women with partner or third-party leukocytes. The risk of transfusion reactions, alloimmunization, infectious disease transmission and untoward fetal effects, implore the use of caution with this treatment. Until recently, there has been no standardization of admission criteria and immunization protocols, so efficacy has been difficult to assess. Meta-analysis of four published, randomized, placebo-controlled trials of immunotherapy by Fraser and colleagues [19••] involving 117 treated women and 129 control women demonstrates that there is fair evidence against its use. Another randomized placebo-controlled trial of immunotherapy for a selected group of women with RPL has since been published and found that therapy bordered on but did not achieve a statistical benefit [20•].

An extensive meta-analysis is now being conducted by the American Society of Reproductive Immunology including both published and unpublished data to further investigate the value of immunotherapy [21•]. Until further elucidation of the safety and efficacy of immunotherapy, interested couples should be referred to research centers, and proper informed consent provided.

Autoimmune

Repetitive pregnancy loss is one presentation of the antiphospholipid syndrome (APS). Other clinical manifestations may include venous or arterial thrombosis as well as autoimmune thrombocytopenia. At least one elevation of an antiphospholipid antibody as well as a clinical manifestation confirms the diagnosis. The two pertinent antiphospholipid antibodies are lupus anticoagulant (LAC) and anticardiolipin (ACL). Whereas ACL can be measured accurately by enzyme-linked immunoabsorbent assays using standards available from the Antiphospholipid Standardization Laboratory (Louisville, Kentucky), LAC requires more fastidious assays. The results of ACL testing are reported in the semi-quantitative terms 'negative, low-positive, medium-positive, and high-positive'. Only medium- or high-positive values are associated with APS.

When an automated activated partial thromboplastin time (APTT) prolongation is used to detect the presence of LAC, the assay must be depleted of procoagulant phospholipids for precision. A sample with an APTT prolongation should be mixed in a 1:1 ratio with normal serum and retested. If the problem is a clotting factor deficiency rather than the presence of LAC, then the APTT will correct. Finally, to confirm that LAC is the cause of a prolonged APTT, the addition of excess phospholipid to the assay should correct the APTT. Antinuclear antibody titers and other autoantibody titers do not consistently predict miscarriage. At this time, among the autoantibodies, only LAC and ACL should be obtained during the evaluation of RPL.

Autoimmunity may play a role in up to 5–10% of women with RPL. While the pathophysiology is unclear, decidual vasculopathy and placental thrombosis are common observations in women suspected of autoimmune RPL. An intriguing line of investigation has demonstrated (in a murine model of APS with RPL), that interleukin-3 serum concentrations are diminished. The addition of exogenous interleukin-3 to these mice appears to avert ischemic placental atrophy and almost completely prevents RPL [22•].

The selective use of cytokines may one day prove to be the most effective treatment for APS in humans. In the meantime, treatment of APS-mediated RPL has been attempted with various combinations of heparin, low-dose aspirin (81 mg/day), glucocorticoids, and intravenous immunoglobulins. To date, the lack of appropriate controls and the inconsistent inclusion criteria and treatment protocols has made a treatment consensus im-

possible. It has been assumed that it is rare for a woman with APS and RPL to reproduce successfully without treatment. Various treatment protocols report successful pregnancies 55–85% of the time. Prednisone and low-dose aspirin, and heparin with or without aspirin have been popular regimens. A critical consideration is that women with APS and their fetuses remain at high risk for complications despite treatment. Branch *et al.* [23] found that one-half of treated women with APS developed pre-eclampsia and one-half suffered fetal distress, while over one-third delivered prematurely and another one-third had small-for-gestational-age infants. Five percent of the cohort also developed thrombosis which included a stroke. One treatment combination that may be particularly hazardous is a combination of heparin and glucocorticoids due to the potential additive risk of osteoporosis [24].

Endocrine factors

Poorly controlled systemic endocrinopathies, such as diabetes and thyroid dysfunction, can probably cause pregnancy loss. However, because severe manifestations of these disorders are found infrequently in populations of women with RPL and are clinically obvious, their overall contribution to RPL is negligible. As there is no evidence that asymptomatic endocrine problems lead to RPL, testing serum thyroid, glucose and prolactin concentrations is unproductive.

Luteal phase inadequacy (LPI) refers to an endometrium that is physiologically incapable of allowing normal implantation or pregnancy maintenance, and has been reported to be present in as many as 40% of cases of RPL. Diagnosis is perplexing because neither serum progesterone concentrations or late luteal phase endometrial biopsies are diagnostically sensitive or specific. Up to 3–4% of fertile controls will have false-positive diagnoses of LPI by the standard endometrial biopsy criteria of late luteal phase biopsies out of phase by at least 2 days in two separate cycles. Because LPI is sometimes diagnosed by endometrial biopsy while concomitant serum progesterone concentrations are normal, and because a myriad of other factors beside progesterone deficiency may contribute to an inadequate endometrium, the endometrial biopsy remains the gold standard test [25].

At this time there are no randomized controlled trials which have indicated a benefit from progesterone treatment for LPI. Balasch *et al.* [26] in a small, non-randomized, non-placebo-controlled trial, found a statistically significant advantage of progesterone suppositories over no treatment for RPL with LPI. Progesterone is usually given as 25 mg suppositories twice daily beginning on the third day after ovulation. If progesterone supplementation is considered, it should only be used in women with RPL who have demonstrated two out-of-phase endometrial biopsies, with the understanding that it is still considered empiric therapy.

Counseling

Several generalizations are pertinent when counseling couples with RPL. First, the older the woman, the higher the risk of even chromosomally normal losses. Second, the later in gestation that previous losses occur, the greater the risk for future pregnancy loss. Third, the outcomes of previous pregnancies influence the risk of future miscarriage. A previous live birth confers a better prognosis than when all previous pregnancies have been losses. Fourth, early ultrasonographic confirmation of fetal heart activity is not as reliable in predicting successful outcomes for couples with RPL compared with couples without a history of repetitive losses. Recent reports find that in women with RPL, early ultrasound detection of fetal heart activity is associated with only about an 80% chance of a live-born whereas ordinarily a live embryo noted by first trimester ultrasonography is associated with a >96% rate of a live birth [27,28]. Fifth, a recent report finds that a history of oligomenorrhea may predict a higher risk for miscarriage [29]. This adds credibility to the claims that elevated preconceptional follicular phase luteinizing hormone serum concentrations may signal a higher risk of miscarriage, because oligomenorrheic women commonly have higher circulating luteinizing hormone concentrations. However, Quenby and Farquharson [29] could not confirm that higher luteinizing hormone profiles correspond to RPL, and the point remains controversial. Sixth, it appears that the more pregnancy losses a couple have, the higher their chance may be of birth defects in future live-born children [30]. This adds to the dispiriting evidence that couples with RPL may also have increased risks for infertility, prematurity and small-for-gestational-age infants [31]. Even when the prognosis is not good, couples will find the information provided by their physicians helpful in guiding their future decision-making.

Evaluation and management

A thorough history should include a detailed obstetrical summary, noting the gestational ages of pregnancy losses and interspersed live births. Family genetic and miscarriage histories are important as well as a complete history of environmental exposures. The possibility of APS should also be explored. Depending on the individual clinical situation, it is not unreasonable to begin an evaluation following two consecutive SABs. A judicious evaluation is outlined in Table 1. Still, the cost of a 'complete' workup may be over US\$ 2000, and the chance of finding an abnormality is reported to be less than 50% in some series.

When RPL is unexplained, frustration may tempt caretakers to offer some form of treatment. Unfortunately, treatments for most suspected etiologies of RPL have not been validated with scientific rigor, so optimal management includes resisting the urge to offer treatments that

Table 1. A suggested evaluation for recurrent pregnancy loss.

History	
1)	Obtain a precise obstetric history noting documentation of gestational ages and patterns of pregnancy losses.
2)	Search for historical evidence of antiphospholipid syndrome such as arterial or venous thromboses and thrombocytopenia.
3)	Scrutinize family histories for patterns of RPL, and investigate consanguinity among family members.
4)	Ascertain potential adverse environmental exposures.
5)	Inquire about possible gynecologic and obstetrical infections.
Physical examination	
1)	Perform a general physical examination noting in particular signs of autoimmune dysfunction and advanced endocrinopathy.
2)	During the pelvic examination, look for evidence of Müllerian abnormalities and diethylstilbestrol exposure.
Testing	
1)	Hysterosalpingogram or hysteroscopy.
2)	Late luteal phase endometrial biopsy (repeat in a subsequent cycle if out of phase).
3)	Karyotyping for both partners.
4)	Lupus anticoagulant and anticardiolipin antibodies.
5)	Other tests if indicated by history and physical examination.

may carry undue risks. It is wise to factor in the strength of association of a presumed cause of a couple's RPL before recommending an empiric treatment. Couples with RPL need compassionate counseling. The fact that couples with even three consecutive unexplained losses have a reasonable chance of having a live-born child on a subsequent attempt, 50–75%, despite the lack of specific treatment, can be quite comforting. Several uncontrolled studies indicate that emotional support and counseling alone may favor successful outcomes [29•].

Conclusion

Systematic evaluation will identify a cause for RPL approximately half the time. Many treatments in current use for specific causes of RPL have been incompletely validated, and therefore require judgement and caution before implementation. When a cause for RPL cannot be determined, complex, expensive testing for possible alloimmune causes has not been useful. Likewise, the value of empiric immunotherapy still awaits confirmation and should be relegated to research centers. Attention to previous menstrual and reproductive histories adds invaluable information for counseling couples with RPL. A realistic appraisal of unexplained RPL currently favors conservative management based on accurate counseling combined with the unlimited availability of emotional support.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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This meta-analysis does not support the current use of immunotherapy for RPL. However, only four published randomized controlled studies were included, each of which used different protocols, thus uncertainty remains regarding the value of immunotherapy.

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Near statistical benefit was shown in this randomized controlled trial of paternal cell immunotherapy involving 19 sequentially paired couples. Their meta-analysis of all four published randomized controlled trials using intravenous paternal cell immunization showed an overall beneficial effect with a livebirth odds ratio of 2.6 with a 95% confidence interval of 1.6 to 4.4.

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Mice immunized with anticardiolipin antibodies acquire the classic manifestations of APS, including RPL. Exogenous interleukin-3 reverses the manifestations. The potential importance of cytokines or growth factors, or both, in the pathophysiology of APS is highlighted. The use of cytokine therapy in humans remains a tempting yet premature undertaking for APS-induced RPL.

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This case series includes four patients with APS who had previously miscarried despite low-dose aspirin and heparin. A more aggressive regimen of aspirin, dipyridamole, prednisone and heparin (or warfarin) resulted in all four women delivering live births, but one developed a vertebral compression fracture.

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A total of 203 consecutive couples attending a Liverpool miscarriage clinic were studied to identify predictive factors for future miscarriages. The most significant predictor was a history of oligomenorrhea but more than three previous miscarriages, maternal age 30 years or more, no previous live births, low luteal phase estradiol levels and the presence of antiphospholipid antibodies also helped predict future miscarriage.

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This case-control study finds a significantly higher risk of birth defects among offspring of couples who have had RPL over normal control couples. However, no specific birth defects associated with RPL could be distinguished. Furthermore, both the cases and controls had birth defect rates within the usual range of 3-4% reported for the general population. Thus, the clinical significance of the finding is debatable.

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